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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,988	02/11/2004	Timothy J. Guzi	OC01617K1	5341

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
MCKENZIE, THOMAS C	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 12/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,988	GUZI ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *44-47,49,50 and 52-54* is/are allowed.

6)☒ Claim(s) *31-43,48,51 and 55-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 9/21/05. Applicant has amended claims 31-38, 41, and 43-53. Applicant has canceled claims 1-30. Claims 54-70 are new. Claims 31-53 were previously rejected.

Response to Amendment

2. Applicants argue that their claim 31 embraces compounds with R = 2-aminopyrimidine, 1-methyl-2-pyridone, and benzimidazole *etc.* in addition to the benzyl and pyrimidylmethyl groups implied by the Examiner's suggested new title and that suggested new title could improperly reflect a limited scope of claims. That argument is persuasive and the title objection made in point #2 of the previous office action is withdrawn. Applicants' cancellation of the relevant claims renders moot the indefiniteness rejections made in points #3 and #4. Applicants' deletion of "solvates" from the claims overcomes the enablement rejection made in point #6.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-36 and 38-40 remain rejected and claims 55, 56, 58, 59, 62, and 63 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify what diseases and treatments applicant is intending to encompass so that "the therapeutically effective amount of at least one compound of claim 1" could be determined, who is "a patient in need of" "inhibiting one or more cyclin dependant kinases", or which diseases are "associated with a kinase". Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite. The passage spanning line 14, page 42 to line 22, page 44 lists an impressive sum of such conditions. However, it uses open language. Is this the entire scope of the therapeutic claims or are there other diseases? Is each disease to use a different amount of drug in the composition or will the same amount be used for all diseases?

Applicants have removed the phrase "cyclin dependant" but have left the phrase "a kinase" in the claims. Thus, the claims are far broader than before. Applicants make a number of arguments concerning the admitted ability of their compounds to inhibit cyclin A dependant kinase 2 enzyme (CDK2). However,

since the rejection is an indefiniteness rejection and not an enablement rejection, further clarification is requested. The issue here is solely one of the scope of the therapy that Applicants intend to practice. Determining whether a given disease responds or does not respond to such a CDK2 inhibitor can only be accomplished through potentially inconclusive clinical research. Suppose that a given drug, which has CDK2 inhibiting properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that therpay of this specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given

e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time-release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related CDK2 inhibitors must be tried before one concludes that therapy for a specific disease does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are CDK2 inhibitors *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property that the second drug is capable. It is common for a drug to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but

upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some very different drug. There are for example, agents in antiviral and anticancer chemotherapy that are not themselves effective, but are effective treatments when the agents are combined with something else.

F. Even the most desired outcome does not unequivocally establish the meaning of the phrase. Our drug alone could be an effective treatment of the disease of interest. One still cannot conclude that the disease cured is a CDK2 mediated disease. What if our drug has a second biological effect in addition to CDK2 enzyme inhibition? It is possible that this second mechanism is responsible for the positive outcome.

Consequently, determining the true scope of the claim will require potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-42 remain rejected and claims 55-70 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any human disease. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with claims 32-40 and 55-70 or to use claims 41 and 42. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The skilled physician would not know how to use composition claims 41 and 42, containing compounds of no known medical use. "The [eight] factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The three main issues are the lack of any correlation between clinical efficacy for disease treatment and Applicants' *in vitro* assay, the state of the prior art, and the breadth of the claims.

There is an *in vitro* assay, drawn to inhibition of cyclin A dependant kinase 2 enzyme (CDK2), described in the passage spanning line 27, page 359 through line 3, page 367 with data on twelve compounds. Applicants do not state and it is not recognized in the therapeutic arts this assay is correlated to clinical efficacy for the treatment of any disease diseases. The state of the clinical arts in CDK2 related diseases is provided by Fischer (Expert Opinion on Investigational Drugs, June 2003). Fischer (Expert Opinion on Investigational Drugs, June 2003) in section 7, psanning pages 962-964 states that in 2003, a year after Applicants effective filing date, the CDK2 inhibitor flavopiridol had failed to show anti-tumor efficacy, the CDK2 inhibitor 7-hydroxystaurosporine had failed to show adequate PK propertities, and the third CDK2 inhibitor roscovitine had not been tested in efficacy trials. The state of the clinical arts in CDK2 related diseases is provided by Fischer (Expert Opinion on Investigational Drugs, June 2003). Fischer (Expert Opinion on Investigational Drugs, April 2005) in section 6, psanning pages 463-466 states that in 2005, three years year after Applicants effective filing date, the CDK2 inhibitor roscovitine stll had not been tested in efficacy trials, the CDK2 inhibitor flavopiridol had failed to show anti-tumor efficacy against renal cancer, the CDK2 inhibitor UCN-1 was about to be studies in ovarian cancer, and BMS-387032 had only been studies in a phase I trial. In section 10, page 469, he

concludes "recent reports have questioined the validity of CDK2 as a good target for ... cancer".

The scope of the claims involves all of the hundreds of compounds of claim 31 as well as the unknown of diseases embraced by the term "a patient in need of" "inhibiting one or more cyclin dependant kinases". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants supply seven references and make the argument "that CDKs do indeed play a role in the regulation of tumor cell progression and cancer. While that well may be the case, "playing a role" is hardly the standard required to establish correlation between the *in vitro* assay used by Applicants and clinical efficacy. "[P]laying a role" could mean that CDK2 activation is a consequence, not a cause of cancer development. Applicants' lone assay is drawn to CDK2, not

all cyclin dependant kinases enzymes and certainly has nothing to do with kinases generally, as now claimed. Thus, Applicants must establish a nexus between that specific enzyme and clinical efficacy not between the class of such enzymes generally.

Applicants have not demonstrated nor have they alleged there is any correlation between the lone *in vitro* assay they disclose in pages 359 through page 363 and clinical efficacy against all cancers or even any specific cancer. Case law is clear on this point. In an unpredictable art, such as cancer therapy, *in vitro* assays may be used for enablement only if there is a well-established correlation between the assay and clinical efficacy.

The issue in *Ex parte Balzarini* 21 USPQ2d 1892 concerned HIV treatment and the Board of Patent Appeals and Interferences wrote "While the in *vitro* testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess in *vivo* utility, the in *vitro* tests were not predictive of in *vivo* efficacy."

The issue in *Fujikawa v. Wattanasin* 39 USPQ2d 1895 was adequacy of *in vitro* testing of inhibitors of cholesterol biosynthesis and U.S. Court of Appeals Federal Circuit wrote, "*in vitro* results, in combination with a known correlation

between such in *vitro* results and in *vivo* activity, may be sufficient to establish practical utility". Such a correlation does not exist in the art of cancer therapy employing CDK2 inhibitors.

In a peripheral issue involving assaying insulin-like growth factor-I ("IGF-I") in *Genentech Inc. v. Chiron Corp.* 55 USPQ2d 1636, U.S. Court of Appeals Federal Circuit wrote "by the critical date, ... [s]pecific binding in an RRA was known by those skilled in the art to be reasonably correlated with the *in vivo* biological activity of IGF-I."

In *Ex parte Bhide* 42 USPQ2d 1441, the Board of Patent Appeals and Interferences wrote, "While in *vitro* or in *vivo* tests would not be the only possible way to overcome our basis for questioning applicants' utility, in *vitro* or in *vivo* tests certainly would provide relevant evidence". The issue in the present case is not the utility of applicants' compounds, which was at issue in *Ex parte Bhide* 42 USPQ2d 1441, but rather the narrower issue of enablement for claims drawn to the treatment of all cancers. Since such a claim is inherently not credible, the standard of proof required for such an assertion must be high.

In a case concerning a DNA sequence encoding a mature human IL-3 protein, *Ex parte Anderson* 30 USPQ2d 1866, the Board of Patent Appeals and Interferences wrote in passing "We question whether one skilled in the art would

accept appellants' *in vitro* test as predictive of *in vivo* results and whether one skilled in the art would know how to use the Pro (8) protein made. ... Should the claims of this application be prosecuted further in a continuing application we urge the examiner to consider the enablement and utility aspects of patentability."

In an anti-tumor application, *Ex parte Aggarwal* 23 USPQ2d 1334, the Board of Patent Appeals and Interferences wrote "there is considerable doubt that those skilled in the art would be willing to accept appellants' in *vitro* tests and in *vivo* tests as established models predictive of utility against tumors in humans. See In *re Jolles*, 628 F.2d 1322, 206 USPQ 885 The examiner had more than adequate reason to doubt the objective truth of the broad statement of utility set forth in appellants' specification."

In the most definitive finding on this issue of the adequacy of *in vitro* assays for clinical claims, *Ex parte Stevens* 16 USPQ2d 1379 the Board of Patent Appeals and Interferences wrote "The examiner's position is based on the supposition that the facts described above evidence a prima facie case of nonenablement with regard to the disclosed utility in light of all the applicable legal precedents. Where as here, the disclosed utility is the treatment of cancer, we agree with this supposition. The examiner has cited Ex *parte Busse*, 1 USPQ2d 1908. In that case, the Board of Patent Appeals and Interferences reviewed the relevant prior

decisions of its reviewing court. We shall not repeat those citations here. Suffice it to say that in every cited case the narrow issue involved was whether or not the evidence of record was based on *in vivo* or *in vitro* studies which were generally recognized by those of ordinary skill in the art as being reasonably predictive of success in the practical utility under consideration, i.e., human or, at least, mammalian therapy."

In a vaccine case, *Ex parte Maas* 14 USPQ2d 1762, the Board of Patent Appeals and Interferences wrote "First, although appellants' specification describes certain in *vitro* experiments, there is no correlation on this record between in *vitro* experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in *vitro* studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals. The burden is on appellants to establish the significance of the in *vitro* experiments set forth in their specification."

Concerning the references, neither Hu (Exhibit I) nor van den Heave (Exhibit II) describes any clinical results with any disease. Neither Hu (Exhibit I) nor van den Heuvel (Exhibit II) discuss Applicants' lone *in vitro* CDK2 assay. Thus, neither can provide the missing nexus between that assay and clinical

efficacy for treatment of any disease. Byrd (Exhibit III) states in the sentence spanning both columns of page 4178 that flavopiridol, a compound structurally not related to those present here, showed "modest activity with 4 patients (11%) attending a partial response" in refractory chronic lymphocytic leukemia. Byrd (Exhibit III) states in the second paragraph, page 4176 that flavopiridol is a "broad cyclin-dependant kinase inhibitor", "seems to be p53-independent", and "down-modulates select antipoptosis genes including *mcl-1* and *XIAP*". Applicants have neither showing of such broad spectrum of enzyme inhibiting activity nor any showing concerning p53 or gene modulation. In any case, while Applicants claim treatment of acute lymphocytic leukemia, there is no present claim to treatment of the disease discussed by Byrd (Exhibit III).

Brown (Exhibit IV) states in the fourth paragraph, page 3971 that "[n]o objective responses [using flavopiridol] were observed in gastric, lung, or colon, and only two response (6%) in renal cell cancer". Applicants have no present claim to renal cancer treatment but do have claims to treatment of esophagus, stomach, lung, and colon cancer. The evidence of Brown (Exhibit IV), although dated in 2005, would appear to favor the Examiner's position.

Alvocibid (Exhibit V) summarizes clinical data with flavopiridol, another name for Alvocibid. Flavopiridol is a 4H-1-benzopyran-4-one compound

containing a 4-piperidinyl ring attached to the 8-position. Benzopyranes are bicyclic heterocycles containing a single oxygen heteroatom. The present claims are drawn to pyrazolo[1,5-a]pyrimidine compounds, which are bicyclic heterocycles containing three nitrogen atoms and no oxygen atom. None of the present compounds have a 4-piperidinyl ring attached to the heterocyclic core. The fourth paragraph, page 2 of Alvocibid (Exhibit V) states the conclusion, "alvocibid should be combined with other chemotherapy". Applicants' claims are not limited to combination therapy. The ninth paragraph, page 10 of Alvocibid (Exhibit V) lists eight cytotoxic agents of which alvocibid potentates the action. This data would appear to date from 2003 and 2004, yet Applicants effective filing date is late 2002. The eight paragraph, page 10 states that alvocibid inhibits protein kinase A, protein kinase C, CDK4, CDK2, and caspase-3. Not only have Applicants failed to demonstrate such activity will all of their claimed compounds, there are no assays in the specification by which such activity could be measured. How do we know that one or more of these activities are responsible for the clinical effects of alvocibid? Perhaps it is the combination of PKC and CDK2 activity, which provides the efficacy? Perhaps it is the combination of PKC and caspace-3 activity and CDK2 inhibitor has nothing to do with the clinical effects of alvocibid?

Seliciclib (Exhibit VI) summaries the clinical effects of seliciclib, a purine compound with a benzylamino group at position 6 and a 2-amino-1-butanol radical at position 2 of the purine ring. While the purine ring does resemble Applicants' pyrazolo[1,5-a]pyrimidine core and the benzylamino group does correspond to Applicants radical NH-R, Applicants claimed and taught R^4 groups, H, halo, and alkyl, are quite different from the side chain found in seliciclib. In fact Applicants forbid the nitrogen atom at this position found in seliciclib. In any event, the clinical data with seliciclib dates from 2004 and 2005. The results of a 2005 trial in NSCLC apparently are found on page 2 of this document, which is missing from the reference supplied to the Examiner. Thus, there is no way to evaluate the evidence supplied by Seliciclib (Exhibit VI).

SNS-032 (Exhibit VII) summaries the clinical effects of BMS-387032, a thiazole compound with a piperazine carboxamide attached in the 2-position. This compound is structurally unrelated to those compounds whose use is presently claimed. BMS-387032 has a monocyclic sulfur containing core, unlike Applicants' bicyclic all nitrogen pyrazolo[1,5-a]pyrimidine core. It has no benzylamino group attached to that core but rather an oxazole attached through a second sulfur atom. No efficacy data against any cancer is found in the summary. The data, from 2003 and 2005 is long after Applicants' effective filing date.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 31-43, 48, 51, and 55-70 are newly provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19, 21-47 of copending Application No. 10/654,546. Although the conflicting claims are not identical, they are not patentably distinct from each other because there are many identical or obvious species in these two

sets of claims. For examples the species of the present claim 48 is found in racemic form in the upper left hand corned of page 19 of the recent amendments to copending Application No. 10/654,546. For examples the species of the present claim 51 is an obvious N-oxide of the species in the upper right hand corner of page claim 27 of the recent amendment to copending Application No. 10/654,546. Line 9, page 4 of copending Application No. 10/654,546 teaches the equivalence of N-oxides and reduced forms of heteroaryl radicals. Additionally, the species in the middle of the last row in page 3 the present recent amendments is an obvious homologue of the species in the lower right hand corner of page claim 18 of the recent amendments to copending Application No. 10/654,546. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' request to have this provisional rejection held in abeyance is noted.

Allowable Subject Matter

6. Claims 44-47, 49, 50, and 52-54 are allowed.

Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date

of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571)

273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

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Primary Examiner
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